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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,391	10/28/2003	Jeffrey Isner	47624-CIP (71417)	6371

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,391	ISNER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' preliminary amendment filed on 7/20/04 has been entered.

Claims 49-68 are pending in the present application, and they are examined on the merits herein.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/265,071, filed on 3/9/1999, now issued US 6,676,937, which claims benefit of the provisional application 60/077,262, filed on 3/9/1998.

Upon review of the specifications of the U.S. Serial No. 09/265,071 and the provisional application 60/077,262 and comparison with the specification of the present application, it is determined that the examined claims are only entitled to the priority benefit of the filing date of 10/28/2003. This is because the originally filed parent U.S. application and the provisional application disclose a method for treating **myocardial ischemia** or **ischemic cardiomypopathy**, and **not other myocardial tissues such as a non-ischemic myocardial tissue or a myocardial tissue suitable for transplantation**. Additionally, there is no written support for in either the parent U.S. application or the provisional application for a method comprising **the step of monitoring at least one cardiac function** (limitation of claims 66-67), or **the step of administering to the mammal of a broad genus of an anti-coagulant before, during, or after administration of the nucleic acid to the mammal** (limitation of claim 61).

Accordingly, pending claims 49-68 are only entitled to the priority date of 10/28/2003 for the reasons set forth above.

Should Applicants overcome the assigned priority date of 10/28/2003 on the issues of any myocardial tissue and any anti-coagulant, claims 49-65 and 68 are only entitled **at best to the effective filing date of 3/9/1999** because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for a concept for a co-administering a broad genus of an angiogenic factor or an effective fragment thereof, particularly SCF, CSF **with** an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.

Claim Objections

Claim 67 is objected to because the abbreviation "NOGA" should be spelled out in full at the first occurrence of the term. Appropriate correction is required.

Claim 68 is objected to because the term "oxidesynthase" should be two separate words. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 58-59, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). For the purpose of a compact prosecution, the examiner assumes that the limitations following the phrase "such as" are part of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 49, 52-56, 60-66 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Isner (WO 97/14307).

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic

liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic proteins include aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxidesynthase (an angiogenic factor), L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2). Isner also teaches monitoring collateral artery development in the medial thigh by angiography (page 21, lines10-25) or measuring calf blood pressure for physiologic assessment (page 22, liens 12-27). The measurement of calf blood pressure is one way of monitoring a cardiac function, and therefore the limitation of claim 66 is met.

The method of Isner is indistinguishable from the claimed method of the present invention, and therefore it is inherent that the method of Isner also produces the desired effects of the presently claimed method.

Accordingly, the Isner reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 49 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Hammond et al. (US Patent 5,880,090; IDS).

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any

injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner do not specifically teach the administration of an effective amount of a stem cell factor (SCF), a colony stimulating factor (CSF) or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though Isner teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Hammond et al already teach that cytokines such as stem cell factor (SCF), granulocyte-macrophage conlony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof in light of the teachings of Hammond et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic factor or protein (page 11, lines 15-19 and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing

the desired therapeutic outcome. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 49 and 66-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Dillmann et al. (US 6,605,274).

The teachings of Isner are already disclosed above. However, Isner does not specifically teach the step of monitoring at least any one of the monitored cardiac function recited in the Markush group of claim 67, even though Isner discloses monitoring collateral artery development in the medial thigh by angiography (page 21, lines10-25) or measuring calf blood pressure for physiologic assessment (page 22, liens 12-27).

However, at the effective filing date of the present application Dillmann et al already teach that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance

studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), Lv end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by monitoring the cardiac function using any of the means recited in claim 67 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Dillmann et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 49, 50-51 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307) in view of Takeshita et al. (J. Clin. Invest. 93:662-670, 1994; IDS).

The teachings of Isner are already disclosed above. However, Isner does not specifically teach the step of administering to the mammal an effective amount of VEGF

or an effective fragment thereof, particularly VEGF-1 or VEGF165, in addition to the injection of an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof; even though Isner teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application, Takeshita et al already demonstrated that therapeutic angiogenesis (e.g., significant augmentation of collateral-vessel development, increased number of capillaries, amelioration of the hemodynamic deficit in the ischemic limb) has been achieved *in vivo* following administration of a recombinant $VEGF_{165}$ (see abstract). Takeshita et al also concluded that the results establishes proof of principle for the concept that the angiogenic activity of VEGF is sufficiently potent to constitute a therapeutic effect (page 669, last paragraph of left-hand column continues to first paragraph of right-hand column).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of a VEGF or an effective fragment thereof in light of the teachings of Takeshita et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is an angiogenic factor or protein (page 11, lines 15-19 and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modification because Takeshita et al. already demonstrated that therapeutic

angiogenesis has been achieved *in vivo* following administration of a recombinant $VEGF_{165}$, and that the angiogenic activity of VEGF is sufficiently potent to constitute a therapeutic, and thus it would ensure enhanced blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner and Takeshita et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49, 52-56, 58-65 and 68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-66 of copending Application No. 10/714,574.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one of: stem cell factor (SCF), colony stimulating factor (CSF) or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal in the copending Application No. 10/714,574 anticipate the claimed genus (a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal) in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PATENT EXAMINER